AMLODIPINE 5MG TABLETS
PL 22903/0004

&

AMLODIPINE 10MG TABLETS
PL 22903/0005

(AMLODIPINE BESILATE)

UKPAR

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AMLODIPINE 5MG TABLETS
PL 22903/0004

&

AMLODIPINE 10MG TABLETS
PL 22903/0005

(AMLODIPINE BESILATE)

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted RIC Chemicals Ltd. Marketing Authorisations (licences) for the medicinal products Amlodipine 5mg Tablets (PL 22903/0004) and Amlodipine 10mg Tablets (PL 22903/0005) on 2nd September 2008. These are prescription-only medicines used for the treatment of high blood pressure (hypertension) and a certain type of chest pain caused by restriction of blood supply to the heart (angina).

The active ingredient is amlodipine besilate. If you have high blood pressure, amlodipine works by relaxing blood vessels, so that blood passes through them more easily. If you have angina, you may get chest pains when your heart cannot get enough blood. This usually happens during exercise or stress. Amlodipine helps to prevent this by increasing the blood supply to the heart. Amlodipine Tablets do not work immediately to stop the chest pain from angina. In adults, for both hypertension and angina, the usual initial dose is 5 mg once daily which may be increased to a maximum dose of 10 mg depending on the individual patient's response.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Amlodipine 5mg Tablets and Amlodipine 10mg Tablets outweigh the risks; hence Marketing Authorisations (MAs) have been granted.
AMLODIPINE 5MG TABLETS
PL 22903/0004
&
AMLODIPINE 10MG TABLETS
PL 22903/0005

(AMLODIPINE BESILATE)

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted RIC Chemicals Ltd. Marketing Authorisations for the medicinal products Amlodipine 5mg Tablets (PL 22903/0004) and Amlodipine 10mg Tablets (PL 22903/0005) on 2\textsuperscript{nd} September 2008. The products are prescription-only medicines.

These are abridged applications for Amlodipine 5mg Tablets and Amlodipine 10mg Tablets. These are two strengths of amlodipine, submitted under Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of their respective reference products, Istin Tablets 5mg and Istin Tablets 10mg (PL 00057/0297 & 00057/0298), authorised to Pfizer Ltd on 18\textsuperscript{th} September 1989. These were the innovator products. The reference products have been authorised in the UK for more than 10 years, so the period of data exclusivity has expired.

Amlodipine 5mg Tablets and Amlodipine 10mg Tablets contain the active ingredient amlodipine, as the besilate. Amlodipine is one of a group of medicines known as calcium channel blockers and is indicated for the treatment of hypertension, the prophylaxis of chronic stable angina pectoris, and the treatment of Prinzmetal’s (variant) angina (when diagnosed by a cardiologist).

Amlodipine inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined.

These applications for Amlodipine 5mg Tablets and Amlodipine 10mg Tablets were submitted at the same time and both depend on the bioequivalence study presented comparing the applicant’s 10mg product with the reference product Istin Tablets 10mg, Pfizer Ltd. Consequently, all sections of the Scientific Discussion refer to both products.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Amlodipine besilate

Nomenclature:
INN: Amlodipine besilate
Chemical name: 3-Ethyl 5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate

Structure:

Molecular formula: C_{20}H_{25}ClN_{2}O_{5}, C_{6}H_{6}O_{3}S
Molecular weight: 567.1
CAS No: 111470-99-6
Physical form: White or almost white powder
Solubility: Slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol, slightly soluble in 2-propanol
Stereochemistry: Amlodipine besilate has one chiral centre

The active substance, amlodipine besilate, is the subject of a European Pharmacopeia (EP) monograph.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin, and therefore comply with the TSE requirements.

An appropriate active substance specification has been provided which is in line with the EP monograph specification. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. A satisfactory Certificate of Analysis has been provided for the working reference standard used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. It is packed into double LDPE (low density polythene) bags, followed by Triple Laminated Aluminium Foil Bags, which are sealed and placed inside HDPE (high density polythene) drums. Specifications and Certificates of Analysis have been provided for the packaging materials used. The polythene bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.
Appropriate stability data have been generated for active substance stored in a container closure system similar to the proposed packaging. This data demonstrates the stability of the active substance and supports a retest period of 24 months when stored in tightly closed containers, protected from light at a temperature below 25°C.

**DRUG PRODUCT**

**Description and Composition**

Amlodipine 5mg Tablets are white to off-white, round, and uncoated, debossed with ‘AM5’ on one side and plain on other side, and contain 5mg of the active ingredient Amlodipine. Amlodipine 10mg Tablets are white to off-white, round, and uncoated, debossed with ‘AM10’ on one side and plain on other side, and contain 10mg of the active ingredient Amlodipine.

Other ingredients consist of pharmaceutical excipients, namely sodium starch glycolate (type A), silica colloidal anhydrous; microcrystalline cellulose, and magnesium stearate. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis (CofAs) have been provided for all excipients.

The magnesium stearate is of vegetable origin. There are no excipients containing material of animal or human origin. There were no novel excipients used and no overages.

**Dissolution profiles**

Satisfactory comparative dissolution profiles were provided for the test and reference products.

**Pharmaceutical development**

Details of the pharmaceutical development of the drug products have been supplied and are satisfactory.

**Manufacture**

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are satisfactory.

**Finished product specification**

The finished product specifications proposed for both release and shelf life are acceptable, and provide an assurance of the quality and consistency of the finished products. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any reference standards used.
**Container Closure System**

The tablets are presented in PVC (polyvinylchloride) / PVDC (polyvinylidene chloride) / aluminium blister strips, each of 14 tablets, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The finished products are packaged in carton pack sizes of 28 tablets.

Specifications and CoAs for all packaging components used have been provided. These are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. Storage conditions are ‘Do not store above 25°C’ and ‘Store in the original package’.

**Bioequivalence Study**

A bioequivalence study was presented comparing the test product, Amlodipine 10mg Tablets, to the reference product, Istin Tablets 10mg, Pfizer Ltd.

An evaluation of the bioequivalence study is found in the Clinical Assessment section.

**Expert Report**

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

**Product Information**

The approved SmPCs, leaflet, and labelling are satisfactory. Colour mock-ups of the labelling have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

**Conclusion**

The test products are pharmaceutically equivalent to the reference products which have been licensed in the UK for over 10 years. The drug products correspond to the current EU definition of a generic medicinal product because they comply with the criteria of having the same qualitative and quantitative composition in terms of the active substance and pharmaceutical form. On this basis, and considering the bioequivalence data provided, the applicant’s claim that Amlodipine 10mg Tablets is a generic medicinal product of Istin Tablets 10mg is justified.

As the test products, Amlodipine 5mg Tablets and Amlodipine 10mg Tablets, meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 10mg strength were extrapolated to the 5mg strength tablets.

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. It is recommended that Marketing Authorisations are granted.
PRECLINICAL ASSESSMENT

These abridged applications for Amlodipine 5mg Tablets and Amlodipine 10mg Tablets were submitted according to Article 10.1 of Directive 2001/83/EC, as amended.

No new preclinical data have been supplied with these applications and none are required for applications of this type. A preclinical overview has been written by a suitably qualified person and is satisfactory.
CLINICAL ASSESSMENT

INDICATIONS
Amlodipine 5mg Tablets and Amlodipine 10mg Tablets are indicated for the treatment of hypertension, the prophylaxis of chronic stable angina pectoris, and the treatment of Prinzmetal’s (variant) angina (when diagnosed by a cardiologist).

In hypertensive patients, amlodipine has been used in combination with a thiazide diuretic, alpha blocker, beta-adrenoceptor blocking agent, or an angiotensin converting enzyme inhibitor. For angina, amlodipine may be used as monotherapy or in combination with other anti-anginal drugs in patients with angina that is refractory to nitrates and/or adequate doses of beta blockers.

The indications are consistent with those for the innovator products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION
The posology is consistent with that for the innovator products and is satisfactory.

TOXICOLOGY
No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY
Pharmacodynamics
Amlodipine is a calcium channel blocker (ATC Code C08CA01)

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1mm ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

Pharmacokinetics
Absorption, distribution, plasma protein binding: After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.
Biotransformation/elimination: The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Use in elderly: The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients.

Pharmacokinetics - Bioequivalence study

The applicant presented a single bioequivalence study comparing the test product, Amlodpine 10mg Tablets, to the reference product, Istin Tablets 10mg (Pfizer Ltd) under fasting conditions. This was a conventional; randomised, single-dose, open-label, 2-way crossover, laboratory blind study designed to assess the bioavailability of the test product versus the reference product under fasting conditions, conducted in 32 healthy adult male subjects. The study was of an appropriate design and was conducted to principles of Good Clinical Practice.

Subjects were administered with a single 10mg dose of test or reference products, following an overnight fast of at least 10 hours. Treatment periods 1 and 2 were separated by a satisfactory washout period of 28 days. Blood samples were obtained at 21 time points up to 216 hours post dose, and plasma amlodipine content was analysed employing a validated LC-MS/MS method. Plasma samples of 30 subjects (1-30) were analysed.

Statistical evaluation was performed for AUC<sub>0-t</sub>, AUC<sub>0-∞</sub>, and C<sub>max</sub> and the 90% confidence intervals for the ratio of test formulation over the reference formulation were calculated. The results of the main pharmacokinetic parameters are summarised below.

Pharmacokinetic results of amlodipine for a randomised single dose crossover study between the test and reference product. Log transformed. N = 30 healthy adult male subjects, dosed fasted; 28 day wash out period

<table>
<thead>
<tr>
<th>Test parameter</th>
<th>Test product (geometric mean)</th>
<th>Reference product (geometric mean)</th>
<th>Ratio Test/reference x 100</th>
<th>90% Confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng.h/ml)</td>
<td>318.030</td>
<td>306.557</td>
<td>103.7</td>
<td>99.65-108.01</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng.h/ml)</td>
<td>348.185</td>
<td>334.524</td>
<td>104.1</td>
<td>99.67-108.69</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>5.278</td>
<td>5.135</td>
<td>102.8</td>
<td>99.51-106.14</td>
</tr>
</tbody>
</table>

The 90% confidence intervals for the log-transformed parameters C<sub>max</sub>, AUC<sub>0-t</sub> and AUC<sub>0-∞</sub> of amlodipine lie within the range 80-125%, such that the test and reference products can be considered bioequivalent after a single dose under fasted conditions.

The pharmaceutical conditions for a biowaiver were met. The 5 mg & 10 mg tablets are dose proportional, manufactured by the same process and possess similar dissolution profiles. Amlodipine also exhibits dose-linear pharmacokinetics in the dose range from 2.5 to 10mg. Therefore, in line with the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the biowaiver was accepted, and the results and conclusions of the bioequivalence study on the 10mg strength were extrapolated to the 5mg strength product.
EFFICACY
No new data are submitted and none are required for applications of this type.

Efficacy is reviewed in the clinical overview. The reference products are established and the applications depend upon the bioequivalence study.

SAFETY
No new data are submitted and none are required for applications of this type.

Safety is reviewed in the clinical overview. The reference products are established and the applications depend upon the bioequivalence study.

EXPERT REPORT
A satisfactory expert report is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)
The approved SmPCs are consistent with those for the reference products and are acceptable.

Patient Information Leaflet (PIL)
The PIL is in line with the approved SmPCs and is satisfactory.

Labelling
The labelling is satisfactory.

CONCLUSIONS
All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and demonstrates the bioequivalence of the test (Amlodipine 10mg Tablets) and reference (Istin Tablets 10mg) products within general acceptance limits. The results and conclusions of the bioequivalence study on the 10mg strength were extrapolated to the 5mg strength product. Therefore, the 5mg strength amlodipine formulation is bioequivalent to its corresponding marketed brand formulation, despite bioequivalence not being assessed explicitly.

Sufficient clinical information has been submitted to support these applications. Marketing Authorisations were, therefore, recommended to be granted on medical grounds.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Amlodipine 5mg Tablets and Amlodipine 10mg Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Amlodipine 10mg Tablets, and the reference product Istin Tablets 10mg (Pfizer Ltd). As the applicant’s products were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 10mg strength were extrapolated to the 5mg tablet strength. Thus, no separate bioequivalence studies were necessary for this strength.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPCs, PIL and labelling are satisfactory and consistent with those for Istin Tablets 5mg and Istin Tablets 10mg.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study, and the valid extrapolation of its results and conclusions, support the claim that the applicant’s products and their respective reference products are interchangeable. Extensive clinical experience with amlodipine is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.
AMLODIPINE 5MG TABLETS
PL 22903/0004

&

AMLODIPINE 10MG TABLETS
PL 22903/0005

(AMLODIPINE BESILATE)

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the marketing authorisation applications on 13th April 2007.

2. Following standard checks and communication with the applicant the MHRA considered the applications valid on 20th June 2007.

3. Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 21st November 2007 and 8th May 2008.

4. The applicant responded to the MHRA’s requests, providing further information for the quality sections on 9th January 2008 and 4th June 2008 respectively.

5. The applications were determined on 2nd September 2008.
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Amlodipine 5 mg tablets is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Amlodipine 5 mg Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Active Substance: Amlodipine besilate
Each tablet contains amlodipine besilate equivalent to 5 mg amlodipine.
For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet for oral administration
Tablets are white to off-white, round, flat faced, radial edged, uncoated debossed with ‘AMS’ on one side and plain on other side.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
• Hypertension
• Prophylaxis of chronic stable angina pectoris
• Prinzmetal's (variant) angina when diagnosed by a cardiologist
In hypertensive patients, amlodipine has been used in combination with a thiazide diuretic, alpha blocker, beta-adrenoceptor blocking agent, or an angiotensin converting enzyme inhibitor. For angina, amlodipine may be used as monotherapy or in combination with other antianginal drugs in patients with angina that is refractory to nitrates and/or adequate doses of beta blockers.
Amlodipine is well tolerated in patients with heart failure and a history of hypertension or ischemic heart disease.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
In adults: For both hypertension and angina the usual initial dose is Amlodipine 5 mg tablet once daily which may be increased to a maximum dose of 10 mg depending on the individual patient's response.
No dose adjustment is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors.

Use in children: Amlodipine tablet is not recommended for use in children.

Use in the elderly: Amlodipine, used at similar doses in elderly or younger patients, is equally well tolerated. Therefore normal dosage regimens are recommended.

Patients with hepatic impairment: See section 4.4 Special warnings and precautions for use.

Patients with renal impairment: Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. Amlodipine is not dialysable.

4.3 CONTRAINDICATIONS
Amlodipine is contra-indicated in patients with a known sensitivity to dihydropyridines, amlodipine or any of the excipients.
Amlodipine should not be used in cardiogenic shock, clinically significant aortic stenosis, unstable angina (excluding Prinzmetal's angina), pregnancy and lactation.
4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use in patients with Heart Failure: In a long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of nonischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo. See section 5.1 "Pharmacodynamic Properties".

Use in patients with impaired hepatic function: As with all calcium antagonists, amlodipine's half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. The drug should therefore be administered with caution in these patients.

There are no data to support the use of amlodipine alone, during or within one month of a myocardial infarction.

The safety and efficacy of amlodipine in hypertensive crisis has not been established.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Amlodipine has been safely administered with thiazide diuretics, alpha blockers, beta blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual glyceryl trinitrate, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycaemic drugs.

In vitro data from studies with human plasma, indicate that amlodipine has no effect on protein binding of digoxin, phenytoin, warfarin or indomethacin.

Special Studies: Effect of other agents on amlodipine

Cimetidine: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

Grapefruit Juice: Co-administration of 240ml of grapefruit juice with a single oral dose of Amlodipine 10 mg in 20 healthy volunteers has no significant effect on the pharmacokinetics of amlodipine.

Sildenafil: When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Special Studies: Effect of amlodipine on other agents

Atorvastatin: Co-administration of multiple 10mg doses of amlodipine with 80mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

Digoxin: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

Warfarin: In healthy male volunteers, the co-administration of amlodipine does not significantly alter the effect of warfarin on prothrombin response time. Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

Cyclosporin: Pharmacokinetic studies with cyclosporin have demonstrated that amlodipine does not significantly alter the pharmacokinetics of cyclosporin.

Drug/Laboratory test Interactions: None known

4.6 PREGNANCY AND LACTATION

Although some dihydropyridine compounds have been found to be teratogenic in animals, data in the rat and rabbit for amlodipine provide no evidence for a teratogenic effect. There is, however, no clinical experience with the preparation in pregnancy or lactation. Accordingly, amlodipine should not be administered during pregnancy, or lactation, or to women of childbearing potential unless effective contraception is used.
4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Clinical experience with amlodipine indicates that therapy is unlikely to impair patient’s ability to drive or use machinery. However, side effects such as dizziness and syncope may interfere with this ability; therefore patients should be warned accordingly.

4.8 UNDESIRABLE EFFECTS

Adverse events that have been reported in amlodipine trials are categorized below, according to system organ class and frequency. Frequencies are defined as: very common (>10%); common (>1%, <10%); uncommon (>0.1%, <1%); rare (>0.01%, <0.1%) and very rare (<0.01%).

<table>
<thead>
<tr>
<th>Blood and the Lymphatic System Disorders</th>
<th>thrombocytopenia</th>
<th>Very Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune System Disorders</td>
<td>allergic reaction</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>hyperglycaemia</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>insomnia, mood changes</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>somnolence, dizziness, headache</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>tremor, taste perversion, syncope, hypoaesthesia, paraesthesia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td></td>
<td>Very Rare</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>visual disturbances</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Ear and Labyrinth Disorders</td>
<td>tinnitus</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>palpitations</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>myocardial infarction, arrhythmia, ventricular tachycardia and atrial fibrillation)</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>flushing</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>hypotension</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>vasculitis</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>dyspnoea, rhinitis</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>coughing</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>abdominal pain, nausea</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>vomiting, dyspepsia, altered bowel habits, dry mouth</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>pancreatitis, gastritis, gingival hyperplasia</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Hepato-biliary Disorders</td>
<td>hepatitis, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis)</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>alopecia, purpura, skin discoloration, increased sweating, pruritus, rash</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>angioedema, erythema multiforme, urticaria</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>arthralgia, myalgia, muscle cramps, back pain</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>micturition disorder, nocturia, increased urinary frequency</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Reproductive System and Breast Disorders</td>
<td>impotence, gynaecomastia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>oedema, fatigue</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>chest pain, asthenia, pain, malaise</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Investigations</td>
<td>weight increase, weight decrease</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>
4.9 OVERDOSE

Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine 10 mg has been shown to significantly decrease amlodipine absorption. Gastric lavage may be worthwhile in some cases. Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use.

Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Calcium Channel Blocker

ATC Code: C08CA01

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

The mechanism of the antihypertensive action is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischemic burden by the following two actions.

1) Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

2) The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal’s or variant angina).

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1mm ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

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A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

In a follow-up, long term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population amlodipine
was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

A randomized double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension."

A total of 33,357 hypertensive patients aged 55 or older were randomized and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including: previous myocardial infarction or stroke (> 6 months prior to enrollment) or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 95% CI(0.90-1.07) p=0.65. Among Secondary Endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% vs 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy. RR 0.96 95% CI [0.89-1.02] p=0.20.

In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5mg dose, and 5.0mg dose of amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant.

The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood have also not been established.

5.2 PHARMACOKINETIC PROPERTIES

Absorption, distribution, plasma protein binding: After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

Biotransformation/elimination: The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Use in elderly: The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

5.3 PRECLINICAL SAFETY DATA

None

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Cellulose microcrystalline
Sodium starch glycolate (Type A)
Silica colloidal anhydrous
Magnesium stearate
6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store in the original package.
Do not store above 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER
Amlodipine 5 mg Tablets are available as:
Printed Carton for 2 x 14 tablets. Printed Aluminium/ White Opaque PVDC/PVC blister, 14 tablets/Blister, 2 Blisters in a carton box.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements

7 MARKETING AUTHORISATION HOLDER
RIC Chemicals plc,
Unit 1, Conqueror Court,
Spilsby Road, Harold Hill,
Romford, Essex RM3 8SB,
United Kingdom
Tel: +44 (0) 1708 378886/379601
Fax: +44 (0) 1708 378869
Email: ricchemplc@aol.com

8 MARKETING AUTHORISATION NUMBER(S)
PL 22903/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/09/2008

10 DATE OF REVISION OF THE TEXT
24/09/2008
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Amlodipine 10 mg tablets is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Amlodipine 10 mg Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance: Amlodipine besilate
Each tablet contains amlodipine besilate equivalent to 10 mg amlodipine.
For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet for oral administration
Tablets are white to off-white, round, flat faced, radial edged, uncoated debossed with ‘AM10’ on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

- Hypertension
- Prophylaxis of chronic stable angina pectoris
- Prinzmetal's (variant) angina when diagnosed by a cardiologist

In hypertensive patients, amlodipine has been used in combination with a thiazide diuretic, alpha blocker, beta-adrenoceptor blocking agent, or an angiotensin converting enzyme inhibitor. For angina, amlodipine may be used as monotherapy or in combination with other antianginal drugs in patients with angina that is refractory to nitrates and/or adequate doses of beta blockers.

Amlodipine is well tolerated in patients with heart failure and a history of hypertension or ischemic heart disease.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

In adults:
For both hypertension and angina the usual initial dose is Amlodipine 5 mg tablet once daily which may be increased to a maximum dose of 10 mg depending on the individual patient's response.
No dose adjustment is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors.

Use in children: Amlodipine tablet is not recommended for use in children.

Use in the elderly: Amlodipine, used at similar doses in elderly or younger patients, is equally well tolerated. Therefore normal dosage regimens are recommended.

Patients with hepatic impairment: See section 4.4 Special warnings and precautions for use.

Patients with renal impairment: Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. Amlodipine is not dialysable.

4.3 CONTRAINDICATIONS

Amlodipine is contra-indicated in patients with a known sensitivity to dihydropyridines, amlodipine or any of the excipients.
Amlodipine should not be used in cardiogenic shock, clinically significant aortic stenosis, unstable angina (excluding Prinzmetal's angina), pregnancy and lactation

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use in patients with Heart Failure: In a long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of nonischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo. See section 5.1 "Pharmacodynamic Properties".

Use in patients with impaired hepatic function: As with all calcium antagonists, amlodipine's half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. The drug should therefore be administered with caution in these patients.

There are no data to support the use of amlodipine alone, during or within one month of a myocardial infarction.

The safety and efficacy of amlodipine in hypertensive crisis has not been established.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Amlodipine has been safely administered with thiazide diuretics, alpha blockers, beta blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual glyceryl trinitrate, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycaemic drugs.

In vitro data from studies with human plasma, indicate that amlodipine has no effect on protein binding of digoxin, phenytoin, warfarin or indomethacin.

Special Studies: Effect of other agents on amlodipine

Cimetidine: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

Grapefruit Juice: Co-administration of 240ml of grapefruit juice with a single oral dose of Amlodipine 10 mg in 20 healthy volunteers has no significant effect on the pharmacokinetics of amlodipine.

Sildenafil: When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Special Studies: Effect of amlodipine on other agents

Atorvastatin: Co-administration of multiple 10mg doses of amlodipine with 80mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

Digoxin: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

Warfarin: In healthy male volunteers, the co-administration of amlodipine does not significantly alter the effect of warfarin on prothrombin response time. Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

Cyclosporin: Pharmacokinetic studies with cyclosporin have demonstrated that amlodipine does not significantly alter the pharmacokinetics of cyclosporin.

Drug/Laboratory test Interactions: None known

4.6 PREGNANCY AND LACTATION

Although some dihydropyridine compounds have been found to be teratogenic in animals, data in the rat and rabbit for amlodipine provide no evidence for a teratogenic effect. There is, however, no clinical experience with the preparation in pregnancy or lactation. Accordingly, amlodipine should not be administered during pregnancy, or lactation, or to women of childbearing potential unless effective contraception is used.
4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Clinical experience with amlodipine indicates that therapy is unlikely to impair patient’s ability to drive or use machinery. However, side effects such as dizziness and syncope may interfere with this ability; therefore patients should be warned accordingly.

4.8 UNDESIRABLE EFFECTS

Adverse events that have been reported in amlodipine trials are categorized below, according to system organ class and frequency. Frequencies are defined as: very common (>10%); common (>1%, <10%); uncommon (>0.1%, <1%); rare (>0.01%, <0.1%) and very rare (<0.01%).

| Blood and the Lymphatic System Disorders | thrombocytopenia | Very Rare |
| Immune System Disorders | allergic reaction | Very Rare |
| Metabolism and Nutrition Disorders | hyperglycaemia | Very Rare |
| Psychiatric Disorders | insomnia, mood changes | Uncommon |
| Nervous System Disorders | somnolence, dizziness, headache | Common |
| | tremor, taste perversion, syncope, hypoaesthesia, paraesthesia | Uncommon |
| | Peripheral neuropathy | Very Rare |
| Eye Disorders | visual disturbances | Uncommon |
| Ear and Labyrinth Disorders | tinnitus | Uncommon |
| Cardiac Disorders | palpitations | Common |
| | myocardial infarction, arrhythmia, ventricular tachycardia and atrial fibrillation | Very Rare |
| Vascular Disorders | flushing | Common |
| | hypotension | Uncommon |
| | vasculitis | Very Rare |
| Respiratory, Thoracic and Mediastinal Disorders | dyspnoea, rhinitis | Uncommon |
| | coughing | Very Rare |
| Gastrointestinal Disorders | abdominal pain, nausea | Common |
| | vomiting, dyspepsia, altered bowel habits, dry mouth | Uncommon |
| | pancreatitis, gastritis, gingival hyperplasia | Very Rare |
| Hepato-biliary Disorders | hepatitis, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis) | Very Rare |
| Skin and Subcutaneous Tissue Disorders | alopecia, purpura, skin discolouration, increased sweating, pruritus, rash | Uncommon |
| | angioedema, erythema multiforme, urticaria | Very Rare |
| Musculoskeletal and Connective Tissue Disorders | arthralgia, myalgia, muscle cramps, back pain | Uncommon |
| Renal and Urinary Disorders | micturition disorder, nocturia, increased urinary frequency | Uncommon |
| Reproductive System and Breast Disorders | impotence, gynaecomastia | Uncommon |
| General Disorders and Administration Site Conditions | oedema, fatigue | Common |
| | chest pain, asthenia, pain, malaise | Uncommon |
| Investigations | weight increase, weight decrease | Uncommon |
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Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine 10 mg has been shown to significantly decrease amlodipine absorption. Gastric lavage may be worthwhile in some cases. Clinically significant hypotension due to amlodipine overdose calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

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5.3 PRECLINICAL SAFETY DATA

None

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Cellulose microcrystalline
Sodium starch glycolate (Type A)
Silica colloidal anhydrous
Magnesium stearate
6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store in the original package.
Do not store above 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER
Amlodipine 10 mg Tablets are available as:
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6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements

7 MARKETING AUTHORISATION HOLDER
RIC Chemicals plc,
Unit 1, Conqueror Court,
Spilsby Road, Harold Hill,
Romford, Essex RM3 8SB,
United Kingdom
Tel: +44 (0) 1708 378886/379601
Fax: +44 (0) 1708 378869
Email: ricchemplc@aol.com

8 MARKETING AUTHORISATION NUMBER(S)
PL 22903/0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/09/2008

10 DATE OF REVISION OF THE TEXT
24/09/2008
PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Amlodipine 5 mg and 10 mg Tablets
Amlodipine besilate

READ ALL OF THIS LEAFLET CAREFULLY BEFORE YOU START TAKING THIS MEDICINE.

• Keep this leaflet. You may need to read it again.
• If you have any further questions, ask your doctor or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

The tablets will be called Amlodipine Tablets in this leaflet.

In this Leaflet:
1. What Amlodipine Tablets are and what they are used for
2. Before you take Amlodipine Tablets
3. How to take Amlodipine Tablets
4. Possible side effects
5. How to store Amlodipine Tablets
6. Further information

1. WHAT AMLODIPINE TABLETS ARE AND WHAT THEY ARE USED FOR

The active ingredient, amlodipine besilate, belongs to a group of medicines called calcium channel blockers.

Amlodipine Tablets may be used to treat:
- raised blood pressure (hypertension) or
- a certain type of chest pain (angina) including Prinzmetal’s (or variant) angina.

If you have high blood pressure, amlodipine works by relaxing blood vessels, so that blood passes through them more easily.
If you have angina, you may get chest pains when your heart cannot get enough blood. This usually happens during exercise or stress. Amlodipine helps to prevent this by increasing the blood supply to the heart. Amlodipine Tablets do not work immediately to stop the chest pain from angina.

2. BEFORE YOU TAKE AMLODIPINE TABLETS

Some people must not take Amlodipine Tablets. Discuss this with your doctor if:

• You think you are allergic to amlodipine or other similar medicines, or to the other ingredients in Amlodipine Tablets.
(These are given at the end of the leaflet).
• You have very severe heart problems (might be known as cardiogenic shock), aortic stenosis (narrowing of the aortic heart valve) or unstable angina.
• You are pregnant or breast feeding.
You should also ask yourself the following questions before you take Amlodipine Tablets.

- Do you have problems with your liver?
- Have you recently had a heart attack?
- Do you have very high blood pressure?
- Do you have heart failure?

If the answer to any of these questions is YES, please speak to your doctor before taking these tablets.

Taking other medicines

Some medicines can affect the way other medicines work. There have been no problems reported with Amlodipine Tablets. However, you must make sure your doctor or pharmacist knows what other medicines you are taking or have recently taken, including any obtained without a prescription.

Contraception

If you are a woman of child-bearing age, you must use adequate contraception all the time you are taking Amlodipine Tablets.

Driving and using machines

Amlodipine Tablets can make you feel dizzy and tired. If you are affected do not drive or operate machinery.

3. HOW TO TAKE AMLODIPINE TABLETS

Always take the tablets exactly as your doctor has told you to. The dose should be on the pharmacy label. Check with your doctor or pharmacist if you are not sure. Do not change the dose or stop taking the tablets without talking to your doctor first.

Amlodipine Tablets are not suitable for children or adolescents (under 18 years old). The tablets should be swallowed with a drink of water. You should try to take your daily dose at about the same time each day.

Adults:

- The usual starting dose is 5 mg a day. This may be increased to a maximum of 10 mg a day.
- The same dose is suitable for the elderly or for people with kidney trouble.
- Amlodipine Tablets are not suitable for children.

If you TAKE MORE Amlodipine Tablets than you should:

If you accidentally take too many tablets, or a child swallows some, contact your doctor immediately or go to your nearest hospital casualty department. Take any remaining tablets and the packaging with you to the doctor or casualty department. If an overdose has been taken there may be signs such as flushing (reddening of the skin), feeling dizzy or fainting.
If you FORGET TO take your Amlodipine Tablets
If you accidentally miss a daily dose, just take the next dose as normal. Do not take a double dose to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Amlodipine Tablets can sometimes cause unwanted side effects, although not everybody gets them.

STOP TAKING THE TABLETS and tell your doctor immediately, or contact the casualty department at your nearest hospital, if you experience the following very rare effects which may be the symptoms of an allergic reaction:

- Swelling of the face, lips, tongue or throat, or difficulty breathing or swallowing, itching, rash, peeling of the skin, extensive reddening and blistering of the skin (Stevens-Johnson’s syndrome).

You may need urgent medical attention or hospitalization.

The following side effects have also been reported:

Common (reported in between 1 in 100 and 1 in 10 people):
- Headache, sleepiness, tiredness, dizziness
- Palpitations, flushing
- Feeling sick, stomach ache
- Water retention (swelling).

Uncommon (reported in between 1 in 1,000 and 1 in 100 people):
- Inability to sleep, mood changes
- Shakiness, numbness, tingling
- Problems with sight, ringing in the ears (tinnitus)
- Breathlessness, runny nose
- Being sick, indigestion, diarrhoea, constipation, dry mouth or strange tastes in the mouth
- Hair loss
- Changes in skin colour, purple blotches on the skin, increased sweating, rash and itching
- Muscle cramps, pain in the back, muscles or joints
- Problems with urination, enlarged breasts in men (gynaecomastia), impotence
- Chest pain, weakness, fainting, general pain or a general feeling of being unwell
- Weight loss or gain.

Very rare (reported in less than 1 in 10,000 people):
- Changes in numbers and types of blood cells detected through a blood test (thrombocytopenia)
• Allergic reaction (see above)
• Raised blood sugar levels
• Loss of feeling in fingers and toes due to nerve problems (peripheral neuropathy)
• Heart attack, irregular heart beat
• Sore rash with fever and itching
• Coughing, abdominal pain, swollen and bleeding gums
• Raised liver enzymes (detected in a blood test), yellowing of the skin or whites of the eyes (jaundice, hepatitis).
• Tell your doctor if you notice or are worried by any of the side effects listed. Tell your doctor or pharmacist if you notice any other effects not listed.

5. HOW TO STORE AMLODIPINE TABLETS
Keep all medicines out of the reach and sight of children.
Do not use the tablets after the expiry date which is stated on the carton and on the blister after EXP.
Store in the original package. Do not store above 25°C.
Do not dispose of medicines in the household waste or water.
Take any tablets you have left over back to your pharmacist to be destroyed. These measures will help to protect the environment.

6. FURTHER INFORMATION
What Amlodipine Tablets contain:
The active substance is amlodipine (as amlodipine besilate).
Each Tablet contains 5 mg or 10 mg of amlodipine.
The other ingredients are microcrystalline cellulose, sodium starch glycollate, silica colloidal anhydrous and magnesium stearate.
Amlodipine Tablets are white to off-white, round, uncoated tablets. The 5 mg tablets are marked ‘AM5’ on one side. The 10 mg tablets are marked ‘AM10’ on one side.
The blister packs contain 28 tablets
The Marketing Authorisation holder is RIC Chemicals plc,
Unit 1, Conqueror Court, Spilsby Road, Harold Hill, Romford, Essex RM3 8SB, United Kingdom.
The tablets are made by Zydus France, 25 rue de Peupliers-92000 NANTERRE, France.
This leaflet was prepared in January 2007.
For any information about these tablets, or to obtain a leaflet in a different format, please contact the Marketing Authorisation Holder.
Tel no: +44 (0) 1708 378886/379601.
LABELLING

Amlodipine 5mg Tablets - Carton for blisters, with Braille

Each tablet contains amlodipine besilate equivalent to 5 mg amlodipine. 
Tablet for oral use. Please read the enclosed leaflet before use. Store in the original package. Do not store above 25°C. Keep out of the reach and sight of children. Use as directed by a doctor.

MA Holder: RIC Chemicals Plc. Unit 1, Conqueror Court, Spilsby Road, Harold Hill, Essex RM2 8SR, United Kingdom

Lot No.: 28 tablets 5 mg

Amlodipine Tablets
Amlodipine Besilate

28 Tablets

Amlodipine 5 mg Tablets
Amlodipine Besilate

28 Tablets
Amlodipine 10mg Tablets - Carton for blisters, with Braille